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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	16

DATE MAILED: 07/01/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/685,061	ROBL ET AL.	
	Examiner	Art Unit	
	Thai-An N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 April 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *51-66, 69-102 and 105-146* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *51-66,69-102 and 105-146* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 October 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicants' Amendment, filed 4/10/03, Paper No. 15. Claims 67, 68, 103 and 104 have been cancelled; claims 51, 61-66, 69, 80-86, 97-102, 105, 113-115, 117-119, 122-124 and 129-131 have been amended; claims 133-146 have been added.

Claims 51-66, 69-102 and 105-146 are pending and under current examination.

Double Patenting

Terminal disclaimers, filed 1/28/03, Paper No. 14, over U.S. Application Nos. 09/260,468 and 09/809,018 are proper and have been entered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 51-66, 69-102 and 105-146 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to methods for producing a nuclear transfer unit having genomic DNA of one ungulate species and mitochondria of a different ungulate species, comprising (i) enucleating an ungulate oocyte (ii) inserting a

differentiated ungulate donor cell, or the nucleus of the cell, into the oocyte under conditions suitable for the formation of a NT unit, wherein the oocyte and the differentiated cell are from different ungulate species; (iii) activating the resulting NT unit; and (iv) culturing the activated NT unit to produce a multicellular structure; wherein the multicellular NT unit develops into an ungulate animal having genomic DNA of one ungulate species and mitochondria of a different ungulate species upon being transferred into a female animal of the same species as the oocyte. In further embodiments, the claims are directed to isolated embryonic cells produced by isolating cells from the NT unit, and ungulate animals developed from the NT unit.

The specification discloses the preparation of nuclear transfer units via a method of nuclear transfer of adult human epithelial cell nuclei into enucleated cattle oocytes to form a nuclear transfer (NT) unit (Figure 1) by electrofusion techniques. The methods disclosed in Example 1 of the specification result in the production of 1 NT unit (16-400 cell stage) according to Table 1, page 42. The specification further teaches that interspecies NT can be used to clone a gaur using cross-species nuclear transfer into an enucleated bovine oocyte, with normal karyo- and phenotypic development through attachment and later stages of fetal growth, with the differentiation of complex tissues and organs (see Example 2, p. 43). In particular, the specification teaches that donor dermal fibroblasts were isolated from an adult male guar. Enucleated bovine oocytes were obtained for nuclear

transfer. Following NT, the fused complexes were then analyzed and the resulting blastocysts were transferred into recipient females. Three fetuses were analyzed for confirmation of genomic origin and fetal fibroblast cell lines were derived. These cells were cytogenetically analyzed and mitochondrial DNA and microsatelliteDNA was also analyzed. The specification teaches that cytogenetic analysis of the cloned cell strains revealed a normal karyotype with a chromosome number of 58, identical to the donor fibroblast (see p. 47, line 29). Microsatellite analysis showed that the cloned cell strains had *gaurus* nuclear background (see p. 48, lines 1-2). Analysis of the mitochondrial DNA (mtDNA) found that no *gaurus* mtDNA was present, and that the mtDNA was contributed to the bovine oocytes.

Applicants argue that the claims as amended are now enabled because they limit the claimed invention to methods and products wherein the resulting multicellular NT unit is able to develop into an ungulate mammal having genomic DNA of one ungulate species and mitochondria of a different ungulate species upon being transferred into a female animal of the same species as the oocyte, as described in the specification. Applicants argue that additional support for this method is provided by Saikhun *et al.*, which successfully describes the production of an animal by cross-species NT, using a nuclear donor cell of bison, and an oocyte of Bos indicus. Applicants argue that the development of NT units produced by the claimed methods would produce fully formed animals, which develops the totipotency of the cells of NT units produced by the claimed method, such that one

of skill in the art would be able to practice the claimed invention. See p. 8 of the Response.

Applicants' arguments have been carefully considered, however, they are not found to be persuasive. Firstly, Applicants' claims, as broadly written are not enabled. The term *ungulate* is a broad term that encompasses a wide variety of animals that would not be considered a single species. Encyclopedia Britannica states that an ungulate is, "Generally, any hoofed mammal." [Ungulate. Encyclopædia Britannica. Retrieved June 24, 2003, from Encyclopædia BritannicaOnline.http://www.search.eb.com/eb/article?eu=76194]. These mammals are composed of four orders, which include, for example, swine, horses and elephants. It is reiterated that the state of cross-species nuclear transfer is unpredictable. In the prior Office action, it was stated that post-filing art supports that nuclear transfer methodology may result in an embryo which contains both paternal and maternal mitochondrial DNA, however, heteroplasmy, as was seen with Dolly, was the result of same-species nuclear transfer. Heteroplasmy can occur between sub-species, as supported by Meirelles *et al.* [cited in the prior Office action] and Shitara *et al.* [cited in the prior Office action]. However, this phenomenon does not necessarily extend to every mammalian species, or to all cell types, which would be used for nuclear transfer [see Shitara *et al.*, *Discussion*, p. 1282]. Furthermore, the cited art of Meirelles *et al.* and Shitara *et al.,* clearly suggests that xenomitochondrial cybrids can be generated, however, due to

incompatibilities and the inability of the cybrid to develop, the cross-species reconstituted embryos fail to develop [see Meirelles *et al.*, pp. 351-352, bridging paragraph]. Accordingly, it is maintained that the claims as broadly written, are drawn to xenomitochondrial cybrids, and the state of the art strongly suggests that even if the claimed invention resulted in an multicellular structure from which an embryonic cell could be isolated and cultured, the mitochondria present in the viable embryonic cells would be from the same species as the donor, *i.e.,* compatible.

Applicants point to Saikhun for support that cross-species NT is enabling, as Saikhun produced an animal by NT using the nuclear donor cell of a bison and the oocyte of Bos indicus. Applicants have not provided this art. However, the Examiner notes that the Saikhun art that Applicant cites does not show the generation of a fully formed animal, as asserted by Applicant [see p. 8 of the specification]. Particularly, Saikhun teach the generation of blastocysts from NT embryos that were cultured *in vitro*. Saikhun fails to teach the transfer of these blastocysts to a recipient female, nor do they teach the generation of a fully formed animal. As such, Saikhun fails to demonstrate that the method of cross-species NT, as presently claimed, would produce fully formed animals and the totipotency of the cells of the NT units produced by the claimed method [see Applicants' Response, p. 8]. As such, it is maintained, as *supra*, that the state of the art of cross-species NT is such that it would not be predictable whether a xenomitochondrial cybrid, as the ones claimed in the instant invention, would be capable of further development into

a fully formed animal. With regard to Applicants' argument that if a cell can produce a fully formed animal, it supports that the cell is totipotent, Gardner [**Int. J. Dev. Bio.**, 41:235-243 (1997)] states that, "[A]lthough nuclei taken from "ES-like cells obtained in several species have been shown to be able to support normal development when transplanted into enucleated oocytes, this does not constitute proof that the cells themselves retain totipotency." See p. 235, 2nd column, lines 3-8.

With regard to claims which specifically state that the differentiated donor cell is from *Bos gaurus* and the oocyte is from *Bos taurus* [see claim 69, for example], the state of the art of interspecific transfer of embryos is unpredictable. In particular, Hammer *et al.* [**Theriogenology**, 55 :1447-1455 (2001)] teach interspecies transfers between *Bos gaurus* and *Bos Taurus.* Particularly the *B. gaurus* IVF-derived embryos were transferred into *B. taurus* recipients. They teach that the pregnancies were highly irregular, and that out of four calves that were born, two were still born and two died shortly after birth. Hammer conclude that, "[I]nterspecies transfer of *in vitro* produced guar embryos into *Bos taurus* are strongly discouraged." See *Abstract.* Hammer teaches that the potential effect of interspecies transfers on the viability of offspring is yet to be determined [see p. 1448, 1st ¶], and teach that the data from their studies is consistent with those obtained from previous guar/Holstein interspecies transfers. They teach that histological examination of the placenta revealed abnormalities suggesting a feto-maternal incompatibility, abnormalities which have been observed in cloned

embryos. See p. 1452, 2nd ¶. They also teach that guar/Holstein interspecies transfers often result in delivery abnormalities, which have been reported with both IVF and cloned embryos. See p. 1452, 3rd ¶. As the claimed invention requires that the NT unit develop into an ungulate animal, the state of the art of interspecific embryo transfer, and with particular regard to guar/Holstein transfer, is unpredictable. In light of the lack of teachings, guidance or working examples provided by the specification with regard to the production of an ungulate animal having genomic DNA of one ungulate species, and the mitochondria of a different ungulate species, and the unpredictability in state of the art for the production of such animals, the claimed invention is not enabled.

With particular regard to the claimed "embryonic cells" [see claims 79-85, for example], it is noted that the specification teaches that the methods of the instant invention result in the production of 1 NT unit of which the specification reports propagates into what appears to be ES-like cell colonies (as determined by cell morphology) in Example 1, and the production of fetal mammals using interspecies NT (Example 2), the specification fails to demonstrate that the ES-like cells function in Example 1 as true ES-cells in that they are in fact totipotent or that they function as stem cells in that they are capable of differentiation into other multilineage cell-types. As such, the specification fails to enable the *production* of embryonic or stem-like cells, which, in further dependent claims [see, for example, claim 75] would be further cultured to produce a cell line. In particular, the claimed

invention is directed to "isolated embryonic cell(s)" which are produced by nuclear transfer methods. It is noted that embryonic cells encompass embryonic stem cells [both totipotent and pluripotent]. However, the specification does not provide teachings or guidance to demonstrate that the cells that are described by the specification as "ES-like" are true pluripotent/totipotent cells (embryonic stem cells or embryonic or stem-like cells). Particularly, the specification fails to demonstrate whether the ES-like cells stain positive for alkaline phosphatase (AP), exhibit the formation of embryoid bodies, spontaneously differentiate into at least two different cell types, or express exclusive ES cell markers. The specification only discloses several morphological characteristics (Example 1). Further, it is not predictable (without specific guidance) whether the described ES-like cells are even cells which are capable of differentiation upon induction to a particular cellular pathway, e.g., lineage or multilineage precursor. The specification teaches that the prior art is lacking in the production of inner cell mass cells from NT units useful to form ES cell-like colonies that could be propagated (page 6, lines 19-22). Thus, the skilled artisan would not have found guidance from the art on the methodology of nuclear transfer utilizing differentiated adult ungulate cells or nuclei for insertion into ungulate enucleated oocytes. For this, the artisan could only rely on the instant specification and in light of the very low frequency of NT units produced by the method, the lack of a showing demonstrating differentiation from the produced cells, and the lack of evidence demonstrating ES cell totipotency; the claimed

invention is not enabled by the specification. Furthermore, as the claimed isolated embryonic cells(s) additionally encompass cells which are not totipotent or pluripotent, Applicants have not provided a use for such isolated embryonic cells. As such, it is unknown how the skilled artisan would be able "to use" the claimed isolated embryonic cells in a manner which is consistent with the specification without specific guidance.

Further, Applicants' arguments have not overcome the unpredictabilities in the art with regard to the species-specific differentiation of ES cells. As such, the specification fails to provide guidance and direction for critical parameters of the claimed invention with respect to obtaining true totipotent embryonic stem cells that give rise to germline tissue and the whole animal, or even embryonic cells which are merely capable of differentiation, for example.

It is reiterated that with regard to the structure and function of the cells produced by the NT methods of the invention, Dominko et al. (Biology of Reproduction, 1999 and cited by Applicant) support that cross-species NT *cannot* be judged as useful before nuclear reprogramming, somatic cell/recipient cytoplasm compatibilities are examined. See page 1501, last paragraph. With regard to examining nuclear reprogramming or dedifferentiation, Dominko et al. disclose that such can only be determined by demonstration of a pregnancy carried to term. As Dominko et al. only teach that bovine cytoplasm has the ability to support several mitotic cell cycles directed by newly introduced nuclear DNA, importantly, they

note that "[w]hether this introduced differentiated DNA is reprogrammed, is modified, or simply remains unchanged is currently under investigation." See page 1501, column 1, first paragraph. As such, in view of the supported undeveloped and unpredictable state of the art with respect to the characterization of cells produced by cross-species NT, Applicants' demonstration of the production of only one NT unit (Table 1) cannot be extrapolated to the production of embryonic stem cells as known in the art or as precursor cells as known in the art.

The courts have stated that:

A specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, **when there is no disclosure** of any specific starting material or **of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement.** Genentech Inc. v. Novo Nordisk A/S, 42 USPQ2d 1005 (CAFC 1997) (emphasis added).

In the instant case, the specification fails to provide guidance to the skilled artisan on any parameters which would be necessary and critical for cross-species NT process from which embryonic cells [which include totipotent, pluripotent cells] can be isolated and cultured to produce cell lines. As such, it would have required undue experimentation for one skilled in the art to perform the claimed methods of

NT transfer for production of cells which meet the criteria of a true embryonic stem cell, or rather a stem cell of sort, which upon differentiation, would provide cellular or gene therapy upon transplantation. A nexus must be provided between the production of their one NT unit and claims directed to "isolated embryonic cells".

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above, the lack of direction and/or guidance provided by the specification, the absence of working examples for the demonstration of or reasonable correlation for producing isolated embryonic cells comprising the genomic DNA of one ungulate species and the mitochondria of a different ungulate species [such cells encompassing embryonic stem cells] which are capable of mere differentiation, for example; the unpredictable and undeveloped state of the art with respect to cross-species nuclear transfer (using adult differentiated nuclei) for production of isolated embryonic cells [of which, embryonic stem cells are encompassed] which give rise to germline tissue and the whole animal or which may be induced to differentiate, in particular with respect to carrying out a process involving insertion of differentiated ungulate cell nuclei into an ungulate oocyte of another species, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 51, 83, 86, 117 as written, are vague. The claim recites that the NT unit has the genomic DNA of one *ungulate species* and the mitochondria of a different ungulate species. The term *ungulate species* is unclear because an ungulate, in taxonomic terms, refers to four orders of mammals [see Encyclopedia Britannica, cited *supra*]. As such an ungulate would not be considered a species. Claims 52-66, 69-81 and 121-139 depend from claim 51; claims 84-85 depend from claim 83; claims 87-102, 106-116 and 140-146 depend from claim 86, claims 118-120 depend from claim 117.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thái-An N. Ton whose telephone number is (703) 305-1019. The examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the examiner be unavailable, inquiries should be directed to Deborah Reynolds, Supervisory Primary Examiner of Art Unit 1632, at (703) 305-4051. Any administrative or procedural questions should be directed to William Phillips, Patent Analyst, at (703) 305-3482. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

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